REMARKS

Claims 1, 5, 6, 9-11, 14-16, 20-24 and 27-29 are now pending. By this Amendment, claims 17-19, 25 and 26 are canceled; claims 1, 6, 9-11, 14, 16 and 27 are amended; and claims 28 and 29 are added.

Claims 1, 5, 6, 9-11 and 14-27 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicant respectfully traverses the rejection.

It is respectfully submitted that the *in vivo* experiments demonstrated in the Declaration filed June 17, 2004, clearly overcome any general teaching that it can be difficult to deliver antisense molecules. However, in an effort to amend the claims to recite a method that is even more clearly enabled by the present specification, claims 1 and 27 have been amended to recite a method of inhibiting invasiveness of metastatic tumor cells of epithelial tissue origin or of inhibiting invasiveness of placental cytrophoblast cells, respectively. It is respectfully submitted that these methods are clearly enabled by the present specification.

In addition, in accordance with the Examiner's request, attached is a brief description of each of the references discussed in the Declaration filed June 17, 2004. It is respectfully submitted that these publications clearly demonstrate the expression of heterologous sequences in cells and in particular antisense therapeutics. Thus, these publications demonstrate that, at the time the present application was filed, there was significant guidance in the art as to how to make and use antisense molecules.

The specification clearly enables the present claims. Therefore, the enablement rejection should be reconsidered and withdrawn.

Claims 1, 5, 6, 9-11, 14-19 and 21-26 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicant respectfully traverses the rejection.

Claims 1, 9, 10 and 27 have each been amended to recite that the nucleotide sequence comprises SEQ ID NO: 7 or a fragment thereof that hybridizes to an RNA sequence of a thrombin receptor, thereby interfering with the process of mRNA translation into protein. It is respectfully submitted that the present application clearly provides written description for fragments of SEQ ID NO: 7, as well as SEQ ID NO: 7.

In particular, the specification specifically indicates that an antisense oligomer of more than 15-17 nucleotides in length would be expected to have a unique sequence relative to the entire human genome. Therefore, a suitable oligomer should be able to interfere, in a sequence specific manner, with the process of mRNA translation into protein. Page 4, lines 16-20. In addition, the original claims are not limited to a sequence comprising all of SEQ ID NO: 7. Thus, the inventors clearly envisioned using less than the entire sequence of the thrombin receptor in an antisense molecule.

The specification clearly provides written description for SEQ ID NO: 7 and fragments thereof. Therefore, the written description rejection should be reconsidered and withdrawn.

Claim 6 is rejected under 35 U.S.C. §112, second paragraph. Claim 6 has been amended to recite the language suggested by the Examiner. Therefore, the §112, second paragraph, rejection should be withdrawn.

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1, 5, 6, 9-11, 14-16, 20-24 and 27-29 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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Registration No. 27,075

Melanie L. McCollum
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JAO:MLM/jam

Attachment:
Brief Description of References

Date: March 1, 2005

OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

SUBMISSION

The following is a brief description of the contents of each of the references mentioned in the Declaration by Rachel BAR-SHAVIT, submitted to the USPTO in connection with U.S. 09/744,679.

Alama A, et al. *Pharmacol Res.* 1997 Sep;36(3):171-8

This reference describes in general antisense technology as an efficient tool for *in vitro* and *in vivo* studies to potently decipher regulatory mechanisms in biologic processes and potential therapeutic agents in: cancer, viral infections and genetic disorders. The use of antisense molecules in oncology, virology, genetic and inflammatory diseases are described. Studies supporting the *in vitro* and *in vivo* applications of this technology are also presented. Moreover, the potential clinical use of antisense therapies is discussed.

Peng H, et al. *AIDS.* 1997 Apr;11(5):587-95

This reference provides an example of a useful application of antisense molecules in treating HIV. The approach is via the construction of a retro viral vector expressing antisense RNA targeted at HIV reverse transcription intermediates. These viral vectors are tested for their inhibitory properties in transduced T cells. Human Jurkat T cells transduced with these vectors were challenged with HIV and monitored for viral RNA, viral DNA and p24 production for 23 weeks. The conclusion from these studies is that a long term inhibition is conferred upon the antisense vector although continuos presence of the viral HIV.

Hirota J, et al. *Biochem J.* 1998 Aug 1;333 (Pt 3):615-9

This reference demonstrates that a stable clone of T-cell Jurkat cell line expressing antisense to inositol 1,4,5 –triphosphate receptor (IP3R) type 1, failed to increase levels of Ca^{+2} and IL-2 production - after TCR stimulation. This is in contrast to such stimulation in the absence of antisense IP3R after TCR stimulation.

Freeman JW, et al. *J Gastrointest Surg*. 1997 Oct;1(5):454-460.

This reference describes the properties of p120 antisense oligonucleotides in a highly tumorigenic human carcinoma cell line; MIA PaCa-2. For *in vitro* studies the growth inhibition assays were determined by the abilities of these oligomers to inhibit cell proliferation. For *in vivo* studies the cells were injected into nude mice and tumors were developed. Then the mice were treated daily with either a control sense or antisense oligomers for up to 40 days. P120 Antisense oligomers inhibited effectively at a concentration of 100 micromol/L the proliferation of MIA PaCa cells. Fifteen days after treatment the control mice tumor size reached a significant difference in tumor volume as compared with the antisense p120 oligomers.

Panegyres PK, and Hughes J. *J Neurol Sci*. 1997 Dec 9;153(1):12-9.

This reference describes a system where seizures are induced upon kainic acid addition. Male Wistar rats were pretreated with antisense or sense c-fos oigonucleotides (the gene c-fos has important physiological and pharmacological properties in the central nervous system) prior to kainic acid 10mg/kg intraperitoneal application. Antisense c-fos inhibited the number of wet dog shakes and the appearance of limbic motor seizures, effects that not seen with nonsense or vehicle.

- Balaji KC, et al. *Urology*. 1997 Dec;50(6):1007-15.

This references described the effect of c-myc antisense oligonucleotides in human prostate cancer cell lines such as LN CaP, PC3 and DU145. Accordingly, cells were incubated with the antisense oligonucleotides (0-10 microM) and the cell cycle status was determined via FACS analysis. The results suggested that c-myc antisense inhibits prostate cancer cell growth and proliferation.

- Sibille E, et al. *Mol Pharmacol*. 1997 Dec;52(6):1056-63.

This reference describes down-regulation of the 5-hydroxytryptamine2A (5-HT2A) receptor by intra-cerebroventricular injection of antisense oligonucleotides resulting in an antidepressant-like effect in mice.